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SO Accounts of Chemical Research (2001), 34(3), 213-221

Materials A La Combi
Despite the challenges, a growing number of corporate and other labs see promise in studying materials combinatorially
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TI Combinatorial and rapid screening approaches to homogeneous catalyst discovery and optimization
AU Crabtree, Robert H.
CS Yale Chemistry, New Haven, CT, 06520-8107, USA
SO Chemical Communications (Cambridge) (1999), (17), 1611-1616 CODEN: CHCOFS; ISSN: 1359-7345

Thanks

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special report

Materials À La Combi

Despite the challenges, a growing number of corporate and other labs see promise in studying materials combinatorially

Ron Dagani
C&EN Washington

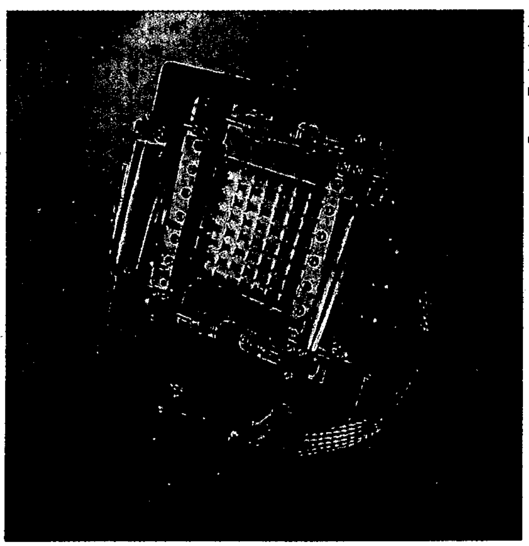
One day, perhaps next year, perhaps sooner, a company will announce that it is marketing a new material—maybe a phosphor, a catalyst, or a polymer—that was discovered and optimized using combinatorial chemistry and high-throughput screening.

That eventuality seems inevitable, considering that a growing number of laboratories and researchers are jumping on the bandwagon known as "the combinatorial approach to materials discovery." These labs are creating libraries, or collections, of materials by reacting a set of components in many different combinations at once. And despite a number of major technical challenges, they are developing techniques by which hundreds or thousands of these materials can be rapidly and automatically screened for desired properties.

This approach allows scientists to accomplish in days what might take years using traditional research methods. At a recent conference, Peter E. Cohan, vice president for discovery tools at Symyx Technologies, the pioneering combinatorial materials company in Santa Clara, Calif., had this to say: "Last year, we designed, synthesized, screened, and analyzed a whopping 1 million entities." Compared to the number of drug candidates that are prepared and screened using related methods in the pharmaceutical industry, Cohan noted, "that sounds like a small number. But in materials science, where typically a pair of scientists does about 560 samples per year, this is a very, very big number."

The ability to synthesize and screen substances at such an unprecedented rate suggests that new materials with superior properties will be discovered more quickly and easily than ever before. Better materials have already been discovered using combinatorial chemistry, but whether they are sufficiently superior to existing materials to become commercial successes remains to be seen.

"Even if successes from industry are very slow in coming, that wouldn't prevent me, say, as a research director, from investing resources in this field, because I think it's impossible to imagine how work in this field isn't going to be valuable," says Anthony W. Czarnik, editor of the *Journal of Combinatorial Chemistry* and a founder of Illumina, San Diego. In the pharmaceutical area, he points out, many companies made "a major commitment to combinatorial chemistry before any compound of value had come out of it."



A device used for screening the thermal and electron-transport properties of semiconductor libraries.

Symyx Technologies

In the fledgling combinatorial materials industry, Symyx Technologies, founded in 1995, has been the powerhouse player. The company has about 200 employees and is entirely focused on using combinatorial and high-throughput methods to develop electronic materials, polymers, homogeneous and heterogeneous catalysts, and other materials.

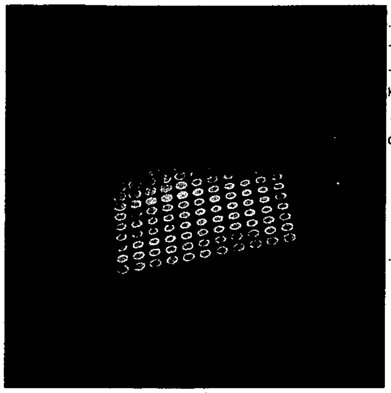
But Symyx isn't alone. Big companies such as Lucent Technologies, General Electric, and DuPont have significant research activity in this area. Other companies dipping their toes in the combinatorial materials field have developed alliances or partnerships with companies that can provide equipment and services for high-throughput materials discovery. For example, Bayer, BASF, Celanese, Dow Chemical, and other companies have partnered with Symyx. And UOP has forged an alliance with Sintef, an independent research foundation in Trondheim, Norway, to speed the discovery of new catalysts and adsorbents.

In addition, new companies focused on the combinatorial/high-throughput approach have been popping up like daisies. For instance, Shell International Chemicals, in a multipartner deal involving other companies and three Dutch universities, has spun off Avantium Technologies, Amsterdam. Catalytica Advanced Technologies, Mountain View, Calif., and CombiChem, San Diego, have begun a joint venture dubbed Aperion Technologies. BASF has begat the start-up hte (for high-throughput experimentation) GmbH in Heidelberg, Germany. And the list goes on.

Government labs, such as Lawrence Berkeley National Laboratory in California; the National Renewable Energy Laboratory in Golden, Colo.; and the National Institute of Standards & Technology (NIST) in Gaithersburg, Md., also have active programs in combinatorial materials, as do many universities.

One of the best ways to find out what's going on in this field—and who's getting into it—is to go to scientific meetings and see who shows up. In the past two years, the number of conferences and symposia on combinatorial materials has "picked up a lot" because "the field is growing rapidly," says John D. Hewes, a project manager at NIST's Advanced Technology Program.

But R. Bruce van Dover, a physicist at Lucent Technologies' Bell Laboratories in Murray Hill, N.J., observes that, even though "there's a huge amount of interest" in combinatorial chemistry at these meetings—evidenced by very well attended sessions—"the number of contributed papers is actually not all that huge." Most of the symposia are quite short, and invited papers outnumber the contributed papers. At last



Symyx Technologies

Library of inorganic phosphors glows under ultraviolet illumination.

month's Materials Research Society meeting in San Francisco, for instance, the combinatorial materials symposium, which van Dover cochaired, was a one-and-a-half-day affair, with 13 invited papers and only eight contributed papers on the schedule. By contrast, most of the other 33 symposia at the meeting extended over three or four days and were heavy with contributed talks.

Van Dover's explanation is that, even though "there's a lot of interest, the number of people who are willing to talk about what they are doing is still small." According to NIST scientists, the combinatorial approach "hasn't really caught on yet" in a big way in academia, perhaps because "it's a very expensive methodology to buy into." And some academics who have plunged into it are in the early stages of their work and don't have that many results to report, van Dover believes.

On the other side of the coin, many industrial researchers are making advances but aren't free to talk about the materials they've discovered. One insider who asked not to be identified offered the following blunt assessment: "A lot of companies are pretty scared about the intellectual property issues—who holds the patents and what's going to happen with the patents. So I would say there are companies—like Symyx—that are holding their cards really close to their vest." Symyx scientists routinely speak at meetings about some of their research in general terms, but "there's a whole lot more that they're doing that they're not talking about," this insider says.

Reluctance to divulge details certainly was a characteristic of the talk Symyx's Cohan gave at the American Chemical Society's ProSpectives conference on combinatorial chemistry last month in Tucson, Ariz. (For coverage of that meeting, see page 53.) One of the projects he mentioned was a combinatorial search for new X-ray phosphors for mammography applications. A number of companies have spent the past 15 years trying to improve on existing phosphor materials, without success, he noted. Symyx researchers prepared and screened about 70,000 phosphor candidates. "We found some very nice compounds that had the performance properties that really made it worthwhile to pursue," Cohan reported. "Our partner, Agfa [an imaging solutions company], intends to commercialize one of these new materials next year. The time line from discovery to commercialization will be on the order of two-and-a-half years." He offered no clues as to the composition of the new materials.

Cohan also mentioned that Symyx researchers have found improved catalysts for alkane oxidation and ammoxidation, and that the company's living free-radical polymerization project has opened the door to a broad range of new materials such as thermoplastic elastomers and amphiphilic materials. And again, no details.

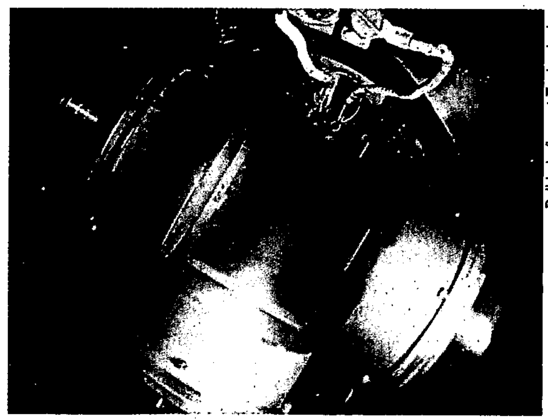
Such reticence is frustrating for many scientists in the field—those who want to hear more about results as well as those who want to be able to say more. "There's a hunger for 'how to,' " remarks Lynn F. Schneemeyer, a materials chemist at Bell Labs. Researchers can choose among a number of different approaches for making materials, and these "have advantages and disadvantages depending on the target you're attacking," she says.

At the same time, Schneemeyer points out, "You don't get much fame and glory for developing a technique" for making materials. "The fame and glory," van Dover chimes in, "is in finding a new material with some neat property for some application."

They should know. Two years ago, van Dover and Schneemeyer, working with Bell Labs physicist Robert M. Fleming, discovered a promising thin-film dielectric—a zirconium-tin-titanium-oxygen compound—using the so-called continuous-composition spread (CCS) technique. In this technique, the metallic components are codeposited from three sputter guns arranged at a 90° or 180° angle from each other around a rectangular substrate. The amount of metal deposited from each gun varies with the distance from the gun. Thus, smoothly varying composition gradients of three metals are produced on the substrate in the presence of oxygen. The intermixing of the elements at relatively low temperatures (below 400 °C) produces the desired amorphous oxide films.

In their search for the new dielectric, the Bell Labs researchers probed the electrical properties of the films at some 4,000 discrete points. Over a three-month period, they evaluated some 120,000 compositions involving a variety of metallic elements. Details of the dielectric discovery were published in *Nature* [**392,** 162 (1998)].

Since then, the team has used the CCS technique to identify other thin-film electronic materials. Presently, they are extending this combinatorial-type parallel approach to search for new optical materials for planar waveguide applications. The materials currently in use are silica and phosphorus-doped silica. Van Dover and Schneemeyer's team is looking for related materials, such as tantalum-doped silica glass, that might provide different functions or the capability to make new circuits.



Bell Labs/Lucent Technologies

Apparatus used to prepare continuous composition spreads at Bell Labs consists of three sputter guns arranged around a square substrate. Each gun deposits a different metal on the substrate in an oxygen atmosphere, forming an oxide film whose composition varies smoothly from point to point. The film is later probed for useful compositions. This is a composite image of the bright glow discharges, which were photographed during a run, and the guns themselves, which were photographed after the run with the top of the apparatus removed.

Continuous-spread approaches also

are being used at other labs, although not necessarily to prospect for new materials. At NIST, for example, researchers J. Carson Meredith, Alamgir Karim, and Eric J. Amis of the Polymers Division are developing methods to study the fundamental properties and behavior of polymer thin films under different conditions. In some of these experiments, they lay down a polymer film whose thickness gradually increases from one side of a wafer to the other. Then a temperature gradient is applied orthogonal to the thickness gradient. An automated microscope is used to observe more than 1,000 sites on the film as a function of time. If the film is not perfectly adherent, pinholes will form in the film as it dewets from, or uncoats, the surface, and these holes can be observed growing larger and larger, explains Amis, who is chief of NIST's Polymers Division. Thus, the film's dewetting behavior—which is of interest for photoresists, paints, coatings, adhesives, and other materials—can be rapidly charted as a function of film thickness, temperature, and time.

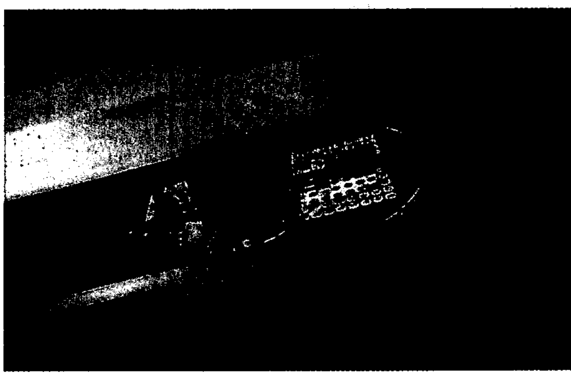
Similarly, by applying a temperature gradient across a thin film having a smooth variation in composition from, say, 100% polystyrene to 100% poly(vinyl methyl ether), the NIST researchers can study phase separation in the film as a function of composition, temperature, and time. "You can chart the phase diagram in an afternoon," Amis says, compared to the weeks needed with traditional methods.

Thanks to the combinatorial approach, Amis adds, scientists can now address materials problems that they wouldn't tackle previously or that they never even thought about before, such as the effect of additives and fillers on the phase diagram.

If combinatorial methods were only for materials discovery, Amis tells C&EN, "NIST wouldn't necessarily play a very big role." But the ability to use this approach to make measurements and create a storehouse of information on materials is "where it becomes a very valuable tool for NIST."

Handling all that data, though, poses a major challenge for the field. "In that afternoon of measuring the dewetting or the phase diagram," Amis explains, "we're creating an enormous amount of information—a gigabyte of image data, which now has to be analyzed. That's not something you can just print out and measure with a ruler. You have to find ways of analyzing those images very quickly and automatically. And then you have to figure out what you're going to do with the data. Do you keep it all?

"And what becomes data?" Amis continues. Initially, you might think you're interested in the fraction of the film that dewets. The next day, you realize you need to know how many holes formed. After that, other questions may pop up: How big were the holes? How fast did they grow? What was their shape? How were they arranged on the surface? Did the shape of the holes change as the thickness or the temperature changed? And so forth.



Symyx Technologies

A library of heterogeneous catalysts is positioned on a motion-control stage under the probe head of a scanning mass spectrometer for rapid screening.

"Knowing how much information you can extract from the raw data is really tough," Amis says. "And, of course, once you've got all that information, how do you turn it into knowledge? How do you put that knowledge into your molecular models" to predict and understand the behavior?

The informatics challenge is not the only one facing researchers using the combinatorial approach. One challenge that is faced earlier in the game is that of high-throughput screening. Large materials libraries may need to be screened for chemical, optical, electronic, and/or mechanical properties. "How do you measure the properties you're interested in in a quick and meaningful way?" Schneemeyer asks.

"Generally," van Dover says, "it's much easier to make the materials than it is to measure their properties." And measuring properties as a function of composition is easier than measuring properties as a function of processing variables. The NIST Polymers Division chemists are doing both, and that, in van Dover's view, is noteworthy.

Symyx's Cohan points out that most polymers are sold and used on the basis of a broad range of properties, including molecular weight, particle size, viscosity, mechanical properties, thermal properties, and rheology. Each of these properties would need to be measured using high-throughput equipment and methods "if a workflow is to be created and sustained," he says.

Another key technical challenge, according to NIST's Hewes, involves systems integration: The hardware tools used to design, fabricate, and characterize libraries need to be integrated with the software tools that control these functions and manipulate the generated data. All of these components are speaking different languages, according to Hewes, and integrating them would improve overall efficiency.

In some areas, such as catalyst development, scientists also face the scale-up challenge: Will a catalyst formed by depositing tiny amounts of inorganic oxides on a silicon wafer work the same as the bulk catalyst on a silicon support in a fluidized-bed reactor? This is not an idle question, Hewes points out, because materials behave very differently on the microscopic scale than they do on the bulk scale.

So far, a clear answer to this question does not appear to be generally available, although Hewes believes that some companies are already putting combinatorially discovered catalysts into scale-up and manufacturing.

Perhaps the most daunting challenge, Cohan suggests, is achieving the cultural change—"moving technical staff as a whole from one-at-a-time to many-at-a-time methods. Symyx was founded completely on the concept of doing everything by combi, but our partners and other companies have enormous inertia" that works against such change. "So it'll be very interesting to see" how quickly this change occurs, he says.

In any case, it's worth keeping in mind that, even if all these challenges are overcome, the combinatorial approach to materials "isn't going to do everything," Amis says. "It's not going to replace traditional methods in most of materials science, but there are some areas where it has great promise."◀

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"The Pluton
ca's Secret
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Eileen Welsor
580 pages, $2
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Reviewed by **Jef**

Simmy, a f boy; Paul, shop forem handyman; Jean others sought m in the years imr after World War stead of healing something else.

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